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STEREOCHEMICAL ASPECTS OF ORGANIC SULPHUR COMPOUNDS OF NATURAL DERIVATION

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Abstract—Selected groups of chiral, tri- and tetra-co-ordinate sulphur compounds are briefly discussed in a historical context. Special attention is given to naturally derived sulphonium salts, sulphoxides, and sulphoximides, and to certain stereochemical problems associated with their structures. The fruitful alliance between biochemistry and stereochemistry, also in studies of sulphur compounds, is emphasized and illustrated. Possible subjects for future studies are adumbrated.

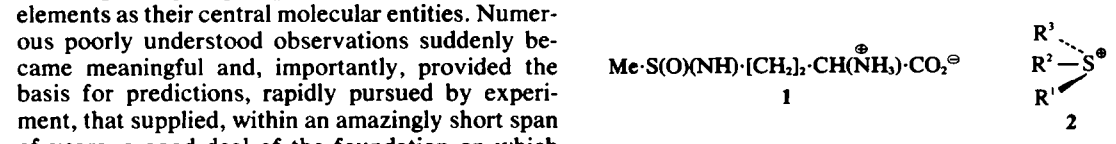
INTRODUCTION

The 100th anniversary of the emergence of a self-consistent, 3-dimensional organic chemistry, founded on the concept of the tetrahedral carbon atom, affords an opportunity to comment also on the massive and almost immediate influence of the event on the chemistry of organic compounds featuring nitrogen, phosphorus, sulphur, and other elements as their central molecular entities. Numerous poorly understood observations suddenly became meaningful and, importantly, provided the basis for predictions, rapidly pursued by experiment, that supplied, within an amazingly short span of years, a good deal of the foundation on which modern stereochemistry safely rests. Organic sulphur chemistry serves well to illustrate the events.

Obviously inspired by Le Bel's reported, but subsequently refuted (Ref 1), asymmetric destruction of methylethylpropylisobutylammonium ion by *Penicillium glaucum*,[2] Smiles, in 1900, communicated the successful resolution of methylethylphenacylsulphonium ion to The Chemical Society.[3] In the same year, Pope and Peachey, independently and as an extension of their celebrated resolution of suitably substituted nitrogen and tin compounds, presented evidence to the Society for the production of methyl ethyl thetin in optically active form.[4] Together, the two communications mark the beginning of a long and unabated exploration of chiral sulphonium ions.

A quarter of a century should elapse before Kenyon, Phillips, and associates succeeded in producing neutral, tri-coordinate sulphur compounds in optically active forms: sulphinates in 1925,[5] sulphoxides in 1926,[6] and *N*-tosylsulphimides in 1927.[7] The knowledge thus aquired constitutes the solid foundation for a good deal of our present understanding of the stereochemical features and interrelations within these classes of compounds.

Yet another leap of 25 years confronts us with methionine sulphoximide 1, first described in 1950 by Bentley *et al.*[8] as the prototype of a novel class of compounds, potentially chiral by virtue of a tetra-coordinate sulphur function. Again, this pioneering investigation signals the beginning of important stereochemical studies within the group of tetra-coordinate sulphur compounds.



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Sulphur stereochemistry at large has been dealt with in several reviews. Here, attention shall be drawn, in particular, to two surveys: Ziegler's chapter in Freudenberg's "Stereochemie",[1] covering the field till about 1930, and the recent treatise by Laur,[9] presenting a commendable, comprehensive account of the actual state of affairs. The goal of the present chapter is a much more limited one: to discuss, in somewhat chronological order, the interesting and notable impetus of biochemistry to sulphur stereochemistry, and *vice versa*, an area with which the author has some personal acquaintance. For practical purposes the ensuing discussion will be conducted under the headings: sulphonium compounds, sulphoxides, sulphoximides, with the main emphasis on stereochemical aspects.

SULPHONIUM COMPOUNDS

As noted above, pyramidal sulphonium ions, with non-identical carbon ligands 2, are chiral entities of long standing. At present, interest in their production,[10] steric stability,[9] and synthetic potentialities,[11] is above par. Surprisingly, however, unequivocal information about the absolute configuration of simple sulphonium ions is still outstanding.

Sulphonium salts occur widely in living cells, often revealing themselves through the odorous sulphides evolved on their exposure to enzymic or chemical degradation. Challenger, in his book from 1959,[12] has given an animated account of the sulphonium compounds in *Nature* up to this time; only a few of these shall be singled out here for additional comments.

Dimethyl-β-propiothetin **3**, reported in 1948[13] as the first,

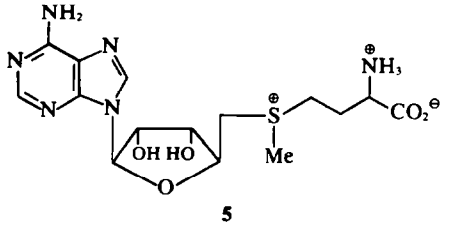
$Me_2\overset{\oplus}{S}\cdot[CH_2]_2\cdot CO_2^{\ominus}$ **3**

$Me_2\overset{\oplus}{S}\cdot[CH_2]_2\cdot CH(\overset{\oplus}{N}H_3)\cdot CO_2^{\ominus}$ **4**

unequivocally identified sulphonium compound in *Nature*, is of unknown biological significance. It shares with other thetins the ability to undergo an enzyme-catalyzed methyl transfer reaction, with L-homocysteine as the receptor molecule.[14] From an experimental viewpoint, specific transfer of one of the enantiotopic methyl groups would hardly be surprising and indeed represents an intriguing, though as yet unproven possibility.

In the same vein, the chiral *S*-methyl-L-methionine **4**, first isolated, in 1954, from cabbage,[15] but present also in many other plants,[12,15] including the jack bean,[16] is accompanied in the latter by an enzyme catalyzing methionine biosynthesis by transfer of a methyl group to L-homocysteine.[17] Though unproven, complete stereoselectivity can be expected in this reaction. In the present case, even transfer reactions, conducted in the absence of enzymes or other external, chiral reagents, may conceivably proceed with notable selectivity. Experiments to test the relative reactivity of the diastereotopic methyl groups in **4**, or analogous compounds, appear inviting. Somewhat surprising, an unpublished ^{13}C-NMR spectrum of the iodide of **4** in heavy water, recorded in the author's laboratory, exhibited only four lines, assigned to C-1, C-2, C-4, and a combination of C-3 and the two methyl C-atoms.

Complete sulphur stereoselectivity prevails in reactions involving *S*-adenosyl-L-methionine **5**, an important biochemical entity. Whereas



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a specimen of **5**, enzymatically synthesized from adenosine triphosphate and L-methionine, was almost completely utilized in the enzymatic methylation of guanidinoacetic acid, another preparation, produced by chemical methylation of *S*-adenosyl-L-homocysteine, was converted only to the extent of about 50% under the same conditions: a clear-cut case of biological resolution.[18] Obviously, only one of the two sulphur diastereomers of **5**, fortuitously produced in almost equal amounts by chemical methylation, is a natural compound and a substrate for the guanidinoacetate methylpherase, as well as other enzymes.[18] Clarification of the absolute configuration of the biologically active isomer of **5** remains an unsolved problem of considerable interest.

Today, the interest in natural sulphonium compounds is growing. As heretofore, biology and chemistry are likely to deal with forthcoming members of the class in unison. Sulphur stereochemistry is almost certain to profit from the alliance, also in the future.

SULPHOXIDES

Sulphoxides became known as natural products in 1948, when Stoll and Seebeck[19] identified alliin, the progenitor of the odorous principle of garlic, as the dextrorotatory isomer of *S*-allyl-L-cysteine sulphoxide **6**. A few months later, Schmid and Karrer[20] established the structure **7** for

$H_2C:CH\cdot CH_2\cdot S(O)\cdot CH_2\cdot CH(\overset{\oplus}{N}H_3)\cdot CO_2^{\ominus}$ **6**

$Me\cdot S(O)\cdot CH:CH\cdot[CH_2]_2\cdot NCS$ **7**

sulphoraphene, an isothiocyanate arising, by enzymic hydrolysis, from a glucoside in seeds of radish. Historically, sulphoraphene deserved attention as the first product of natural derivation exhibiting optical activity solely due to dissymmetry not involving carbon atoms. Today, each of the nine members of the homologous mustard oils **8**, n = 3–11, belonging to the same stereochemical series, is known as a product arising from enzymic hydrolysis of glucosidic progenitors in plants of the crucifer family.[21,22]

$Me\cdot S(O)\cdot[CH_2]_n\cdot NCS$ **8**

$Me\cdot S(O)\cdot CH_2\cdot CH(\overset{\oplus}{N}H_3)CO_2^{\ominus}$ **9**

In 1956, cabbage and turnip, two important crucifer crops, were independently recognized as sources of dextrorotatory *S*-methyl-L-cysteine sulphoxide **9**.[23,24] Within the same year, Hine and Rogers[25] demonstrated, by X-ray diffraction, that (*S*)-configuration prevails around sulphur in the

natural amino acid: the first absolute configuration of a sulphoxide had been determined. This accomplishment, announced 30 years after a sulphoxide was first resolved,[6] helped to precipitate a wave of interest in sulphoxide stereochemistry that has not yet shown signs of abatement (*cf* Ref 9). Once again, natural product chemistry served well in its role as an initiator.

Similarly, X-ray analysis of the dichiral thiourea **10**, produced from the naturally derived mustard oil **8** (n = 3) and (*R*)-1-phenylethylamine, served to define the absolute configuration of the sulphoxide isothiocyanates **8** as (*R*),[26] *i.e.* opposite to that of the amino acid above. Assuming enzymic sulphide oxidation to be a common step

$$Me{\cdot}S(O){\cdot}[CH_2]_3{\cdot}NHCSNH{\cdot}CH(Ph)Me$$

10

$$Me{\cdot}S(O){\cdot}[CH_2]_2{\cdot}CH(\overset{\oplus}{N}H_3)CO_2^{\ominus}$$

11

on the anabolic pathways to the two series of natural sulphoxides, the operation of enzymes with opposite stereopreference within species of the same plant family is evident.

Dextrorotatory L-methionine sulphoxide **11** is a genuine constituent of the blowfly (*Phormia regina*).[27] (*S*)-Configuration around its sulphur center follows from the established enantiomeric relationship between its decarboxylation product, (+)-3-methylsulphinylpropylamine, and the sulphinylamine affording (*R*)-3-methylsulphinylpropyl isothiocyanate in a synthetic sequence.[28]

The list of known, dissymmetric sulphoxides of natural derivation is long and steadily increasing, today encompassing, *inter alia*, several oxidized *S*-substituted L-cysteine derivatives, both linear and cyclic; two biotin sulphoxides; oxidized *S*-methyl vinyl units in polyynes from higher plants; oxidized sulphur-containing terpenes; and linear or cyclic thiolsulphinates. For the majority of these sulphoxides, stereochemical specification remains a challenge.

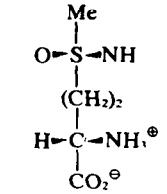
Deliberate attempts to utilize aerobic, microbial oxidation for converting achiral, unsymmetrical thioethers into optically active sulphoxides have been moderately successful. While showing great promise with certain substrates, species and strains, the biological oxygen atom-transfer, in other cases, leaves much to be desired regarding chemical yields and stereoselectivity.[29] Further studies along this line should be encouraged, however. The opening of an easy and broad avenue to sulphoxides in high optical purity would indeed amount to a major and long desired step forward. Perhaps biochemistry shall here, once again, prove its ability to make life easier, also for the organic chemist.

SULPHOXIMIDES

In 1946, Mellanby[30] attributed a condition in dogs, 'canine hysteria', characterized by bouts of hysterical barking, aimless running, and epileptiform fits, to a factor present in the nitrogen trichloride treated flour fed to the animals. Four years later, three groups of workers[8,31,32] had isolated the toxic factor and shown it to be a derivative of methionine, two of the three further specifying the structure as methionine containing one additional atom of each hydrogen, nitrogen, and oxygen. Experimental evidence soon established **1**, *i.e.* methionine sulphoximide, as a correct, general expression for the toxic factor.[33,34] Much immanent novelty was contained in this formulation: sulphoximides were previously unknown in the chemical literature; hence, a new class of compounds has been brought to light. Moreover, the existence of tetra-coordinate sulphur compounds, with non-identical ligands, was unprecedented by 1950; the obvious stereochemical consequences of the sulphoximide structure, as present in methionine sulphoximide, were indeed envisaged,[8] though not convincingly demonstrated, by its discoverers.[33,34]

Shortly after the toxic factor in NCl_3-treated flour had been identified, general methods for the synthesis of sulphoximides, including that of methionine, appeared. The road was now open to the separation of diastereomers of an *N*-sulphonylsulphoximide, with asymmetry built into the sulphonyl substituent,[35] as well as to resolution proper of a monochiral *N*-sulphonylated[36] or even a simple, nonsubstituted sulphoximide.[37]

The absolute configuration of sulphoximides posed an interesting problem. Let us briefly return to the important case of methionine. A mixture of 2(*S*),S(*S*)- and 2(*S*),S(*R*)-methionine sulphoximide, obtained from an approximately 1:1 combination of epimeric L-methionine sulphoxides, in practice inseparable by chromatography or fractional crystallization, could be divided into the individual diastereomers when recourse was taken to salt formation with (+)-camphor-10-sulphonic acid.[38] The epimer, forming the least soluble salt in ethanol-ethyl acetate (1:3), was established, by X-ray diffraction, to possess the 2(*S*),S(*R*)-configuration **12**; the absolute configurations of the other stereoisomers of **1** followed automatically.[38,39]



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Though the toxicity of the pure stereoisomers have not yet been tested in animals, a remarkable biological specificity has been noted with regard to the long known inhibition of brain glutamine synthetase by methionine sulphoximide. Only the 2(*S*), S(*S*)-isomer caused inhibition, suggesting that the supposed multipoint attachment of the substrate to the enzyme is highly dependent on conformational, and hence configurational, features.[40]

Within recent years, sulphoximides have been extensively studied, notably as partners in stereochemical substitution cycles at sulphur, and as reagents for organic synthesis.[41] A continued, perhaps even increasing activity in chemical and biochemical studies of sulphoximides and, most likely, other tetra-coordinate sulphur compounds can be envisaged. Here again, and most emphatically, studies of processes in living matter opened up vistas to novel, intriguing, and, possibly, practically useful organic chemical knowledge.

EPILOGUE

The concept of the tetrahedral carbon atom, today almost a truism, has been our heritage for a century now. It seems appropriate on this occasion to reflect upon the circumstances under which the concept came to life; but also to enquire into its impact on other areas of chemistry than that for which it was originally designed. Sulphur chemistry is such an area. The present essay, brief, and arbitrary in its delimitation, had as its only object to provide a few illustrations of how successfully the tetrahedral carbon model was adopted in sulphur chemistry, thus helping to clarify many structures and processes of vital importance for the proper functioning of living cells.

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